BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

REMARKS

Original claims 1-45 are cancelled and claims 46-73 are added. The added claims are consistent with Group II identified in the restriction requirement issued in the parent case, Application Serial No. 23,002 (Paper 11) (copy included as Appendix A).

The added claims are not new matter. Support for the amendments can be found in the specification at least on page 7, line 31 to page 8, line 11; page 9, line 23 to page 10, line 6; page 12, lines 5-15; page 15, lines 12-25; page 38, line to page 39, line 19; page 62, lines 1-15; and in the originally filed claims.

It is believed that no fee is due; however, should any fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason, the Commissioner is authorized to deduct the fees from Fulbright & Jaworski L.L.P. Account No.: 50-1212/INRP:050USC1.

Respectfully submitted,

Gina N. Shishima
Reg. No. 45,104
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 474-5201
(512) 536-4598 (facsimile)

Date: May 26, 2004

INGN:008

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/233,002	04/25/94	ROTH J	UTSC403PAR

EXAMINER	
~~MILNE,H~~	
ART UNIT	**PAPER NUMBER**
1804	11

DATE MAILED: 11/09/95

18M2/1109

DAVID L PARKER
ARNOLD, WHITE & DURKEE
P O BOX 4433
HOUSTON, TX 77210-4433

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 (three) month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 26-31 are pending in the application.
   Of the above, claims 1-25, 32-45 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 26-31 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

Response
DOCKETED
FOR 2-9-95
BY Cra
CNTD. BY

REC'D - A.W.D.
NOV 16 1995
DOCKET DESK

P20879
COMPUTER INPUT

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

Claims 26-31 are currently pending in U.S. Patent Application Number: 08/233,002.

During a telephone conversation with Shelly Fussey on 7/11/95 a provisional election was made without traverse to prosecute the invention of Group II, claims 26-31. Affirmation of this election must be made by applicant in responding to this Office action. Claims 1-25 and 32-45 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-25, drawn to method of killing cells comprising contacting cells with p53 or gene expression protein, classified in Class 530, subclass 23.5.

II. Claims 26-31, drawn to method of killing cells and treating cancer in vivo, classified in Class 530, subclass 352.

III. Claims 32-41, drawn to a composition of DNA or protein, classified in Class 536, subclass 23.5.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as a process of killing a cell and a process of killing a cell in vivo. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the

product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case, there are many distinguishable characteristics attributable to *in vivo* cancer treatment that separate it from either general or *in vitro* treatment, such as vector constructs that can be used for the successful transformation of cells *in vivo*.

Inventions II and III are related as a process of use and a composition that is to be used. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case, the in vivo treatment of cancer differs from the composition of a protein and a DNA damaging agent, in many aspects; for example, the routes of administration required for proper gene transfer.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as a result of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the

> invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure. Applicants claim a method of killing selected cells through the simultaneous use of DNA damaging agents and a tumor suppressor gene that has been transferred via an adenoviral vector into cells that have been selected for killing. Others skilled in the art are not likely to accept that the simultaneous use of p53 gene therapy and DNA damaging agents will be successful to the point where it would be considered therapeutic and further, that the gene transfer and the DNA damaging agents can be consistently selective as to the cell types that they transform and/or kill.

Given the state of the art and lack of guidance in the specification, others skilled in the art are not likely to accept that the adenovirus will have the ability to express its exogenous genes for a period of time that would be considered therapeutic by one of skill in the art. The Neve reference states on page 252:

> "The investigators attributed the decline in expression to a number of possibilities, including gradual inactivation of the RSV or CMV promoters used or, in the other extreme, toxicity due to usurping of host cell transcription/translation machinery by the strong CMV promoter. Bajocchi et al who targeted the expression of the recombinant lac Z gene to ependymal cells lining the lateral ventricles, noted that expression of foreign genes from adenovirus vectors is often determined by the life

span of the target cells. Given the known stability of the B-gal protein, which can persist in eukaryotic cells long after translation of the protein has ceased, the loss of lac Z expression observed by these groups might have been underestimated. The use of brain-specific promoters might help to resolve this problem and will have the added benefit of allowing increasingly precise targeting of expression to particular cell types within the region surrounding the locus of injection. However, equally likely explanations for the loss of B-gal activity in the adenovirus-infected brains include the possibility that the vector slowly kills the infected cells, for example by triggering an immune response to the infected cells, or that the cells clear it."

It is therefore concluded that in light of the quantity of experimentation necessary, the lack of adequate direction or guidance presented, the lack of correlatable working examples, the nature of the invention, the state of the prior art with its recognized unpredictability, and the breadth of the claims, it would require undue experimentation for others skilled in the art to practice the invention.

Claims 26-31 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which

the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 26-31 are rejected under 35 U.S.C. § 103 as being unpatentable over Perricaudet as taken with Bacchetti in view of Tishler and further in view of Culver.

Perricaudet el at disclose that at the time that the invention was made, the method of transforming cells in vivo through the use of an adenoviral vector was common knowledge to one of ordinary skill in the art. The reference does not however,disclose the transduction of cells with the p53 protein or a gene that codes for it, nor does the reference discuss the simultaneous use of any DNA damaging agents with the adenoviral vector.

Bacchetti et al disclose the use of an adenoviral vector, expressing the wild type p53 protein utilized to infect human cells. The reference further discloses the inhibition of cell proliferation and DNA synthesis upon expression of the p53 protein. The reference does not teach the simultaneous use of DNA damaging agents; however, the deficiency is cured by Tishler et al who teach the effects of chemotherapeutic and DNA damaging agents on binding of p53. Tishler et al disclose that an increase in exposure to ionizing radiation to malignancies

results in elevated levels of p53. The reference further teaches the activation of p53 by the DNA-damaging compound cisplatin, page 2213. The reference does not utilize an adenoviral vector for infection of cells, yet it does disclose that at the time that the invention was made, the activation of the phosphoprotein, p53, was observed upon exposure of cells to chemotherapeutic or DNA damaging agents, thereby providing motivation for one of ordinary skill in the art to use such DNA damaging agents in attempts to activate p53 whether the phosphoprotein was already in a cell and functional, or inserted via a recombinant viral vector.

The method of direct in vivo injection was disclosed by Culver et al who injected a retroviral vector, which did not contain the gene that coded for p53, into a tumor site in the brain, thereby providing an approach to tumor treatment recognized as efficient to one of ordinary skill in the art.

Therefore, it is concluded that at the time that the invention was made, one of ordinary skill in the art would have had sufficient motivation to combine the in vivo adenoviral vector system, as seen in Perricaudet, and to modify the vector so that the resulting expression product would have been p53, as seen in Bacchetti, and further to expose the cells to irradiation and cisplatin in attempting to activate the p53 protein that was being expressed in the animal, because this would have resulted in a maximum arrest in the growth of a malignancy according to

the knowledge displayed by those of ordinary skill in the art. It would have been further obvious to use the efficient method of direct intratumoral injection as seen in Culver, but to use an adenoviral vector system in place of the retroviral vector system because of the adenoviruses' high transduction efficiency.

Any inquiry concerning this communication from the examiner should be directed to Andrew Milne, whose telephone number is (703) 305-7519. The examiner can normally be reached from 7:00 to 4:00 (Eastern Standard Time) Monday thru Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jacqueline Stone, can be reached at (703) 308-3153. The fax number for art unit 1804 is (703) 308-4312.

Any inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is (703) 308-0196.

Andrew Milne
August 31, 1995

JACQUELINE M. STONE
SUPERVISORY PATENT EXAMINER
GROUP 1800